J Clin Oncol 1999 Feb;17(2):585-92

Phase I-II study of gemcitabine and fluorouracil as a continuous infusion in patients with pancreatic cancer.

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PURPOSE: To determine the maximum-tolerated dose (MTD), dose-limiting toxicities, and efficacy of gemcitabine combined with fluorouracil (5-FU) in patients with pancreatic cancer. PATIENTS AND METHODS: Patients with measurable, locally advanced, nonresectable or metastatic pancreatic cancer were candidates for the study. 5-FU was given via protracted venous infusion (PVI) at a fixed dosage of 200 mg/m2/d, and gemcitabine was administered weekly for 3 consecutive weeks every 4 weeks. The initial dose of gemcitabine was 700 mg/m2 and was escalated in increments of 100 mg/m2/wk until the appearance of severe toxicity. Measurements of efficacy included the following: response rate; clinical benefit response, which is a composite measurement of pain, performance status, and weight loss; time to disease progression; and survival. RESULTS: Twenty-six patients received a total of 109 courses. Dose-limiting toxicity, which consisted of grade 4 neutropenia with fever (one patient) and grade 4 thrombocytopenia (one patient), was observed in two of three patients treated with 1,100 mg/m2/wk of gemcitabine. On the basis of these results, the MTD of gemcitabine with 5-FU via PVI on this schedule was 1,000 mg/m2. Sixteen patients developed grade 3-4 neutropenia, and three patients developed grade 3-4 thrombocytopenia. Grade 3-4 nonhematologic toxicity consisted of diarrhea (two patients) and cutaneous toxicity, asthenia, edema, mucositis, and nausea and vomiting (one patient each). The delivered dose-intensity of gemcitabine was similar at the 1,000 mg/m2 dose level (599 mg/m2/wk) as at the 900 mg/m2 (601 mg/m2/wk) dose level. For this reason, the recommended dose of gemcitabine for phase II evaluation on this schedule was 900 mg/m2. Five patients had objective responses (one complete response and four partial responses; response rate, 19.2%; 95% confidence interval [CI], 6.5 to 39.3), and 10 patients had improvement of disease-related symptoms (45%; 95% CI, 24 to 67). After a median follow-up of 17.7 months (range, 7.8 to 24.8 months), the median progression-free survival and overall survival times were 7.4 months (95% CI, 3.3 to 11.4) and 10.3 months (95% CI, 8.1 to 12.5), respectively. CONCLUSION: The MTD of gemcitabine when combined with 5-FU via PVI on this schedule was 1,000 mg/m2/ wk; however, on the basis of administered dose-intensity, the recommended dose for additional investigation is 900 mg/m2. This combination chemotherapy regimen was well tolerated and showed promising antitumor activity in the treatment of pancreatic cancer.